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PBDE Flame Retardants and Thyroid Hormones during Pregnancy

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Chevrier et al. (2010) assessed the association between 10 polybrominated diphenylethers (PBDEs) and free and total thyroxine (T_4) and thyroid-stimulating hormone (TSH) in 270 women around the 27th week of gestation. They concluded that PBDEs are associated with lower TSH levels during pregnancy, but several factors that likely influenced the results were not considered in their analysis.

Normal pregnancy can lead to low TSH levels without affecting T_4 levels, as can several other factors (e.g., starvation; stress; psychiatric disorders; depression; acute or chronic non-thyroidal disorders; alterations in thyrotropin-releasing hormone, cortisol, opiodergic, dopaminergic, or somatostatinergic activity; and alterations in leptin and cytokine production) (Braverman and Utiger 2000; Krassas et al. 2010). None of these were included in the analyses of Chevrier et al. (2010), yet any of them could have contributed to lower TSH levels.

Chevrier et al. (2010) classified women in their second and third trimesters as having subclinical hyperthyroidism if their serum TSH levels were < 0.5 mIU/L and < 0.8 mIU/L, respectively. Krassas et al. (2010) recently reported TSH reference ranges: 5th percentiles for the second and third trimesters were 0.03–0.39 and 0.13 mIU/L, respectively, suggesting that the cutoffs used by Chevrier et al. (2010) led to an incorrect classification of at least some women.

Chevrier et al. (2010) reported that blood was drawn at 27.3 ± 3.1 (mean \pm SD) weeks gestation; however, it is unclear which women were in the second trimester and which were in the third trimester. Although Chevrier et al. (2010) adjusted for gestational age, the use of different cutoffs for a binary variable (subclinical hyperthyroidism) for women in the same analyses likely biased results, particularly considering that differences between women near the end of the second and beginning of the third trimester are not great.

With the exception of a few outliers, the range of each PBDE among study subjects was quite small (all with the ratio of the 75th to the 25th percentile < 3.4). Because blood was drawn only once and all associations noted were quite weak, even a small difference between the measured PBDE level and the actual level in an individual could have biased the results.

All of the PBDE congeners were moderately to strongly intercorrelated ($r = 0.6$ – 0.9 ; $p < 0.001$), yet analyses were conducted only by individual congener, leaving the inappropriate impression that several of the PBDE congeners may have been causally associated with lower TSH levels.

The limitations discussed above preclude one from drawing conclusions regarding associations between serum PBDEs and TSH. It is notable, however, that even if associations are shown to be causal, the decrements in TSH reported are very small and mostly within the reference range for pregnant women. Thus, they are unlikely to result in adverse health effects in either pregnant women or their fetuses.

The views and opinions expressed in this letter are those of the authors and not necessarily those of their respective employers.

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REFERENCES

- Braverman LE, Utiger RD, eds. 2000. Werner & Ingbar's The Thyroid: A Fundamental and Clinical Text. 8th ed. Philadelphia: Lippincott Williams & Wilkins.
- Chevrier J, Harley KG, Bradman A, Gharbi M, Sjödin A, Eskenazi B. 2010. Polybrominated diphenylether (PBDE) flame retardants and thyroid hormone during pregnancy. Environ Health Perspect 118:1444–1449; doi:10.1289/ehp.1001905 [Online 21 June 2010].
- Krassas GE, Poppe K, Glinos D. 2010. Thyroid function and human reproductive health. Endocr Rev; doi:10.1210/er.2009-0041 [Online 23 June 2010].

PBDE Flame Retardants and Thyroid Hormones: Chevrier et al. Respond

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Goodman et al. raise concerns regarding our study (Chevrier et al. 2010) in which we reported associations between serum levels of polybrominated diphenyl ethers (PBDEs) and lower thyroid-stimulating hormone (TSH) in pregnant women participating in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) cohort study. The points they raise are unlikely to have affected the validity of our conclusion.

Goodman et al. correctly point out that, as for most health outcomes, thyroid hormone levels may be affected by a number of factors. However, these factors must be related to PBDE serum levels to confound the associations that we reported. Although it would be of interest to evaluate associations between exposure to PBDEs and the adverse health effects cited by Goodman et al. (e.g., psychiatric disorders, depression, neurotransmitter and hormonal alterations), we are aware of no study that investigated these relationships. Furthermore, should PBDEs cause these health effects, they would be on the causal pathway between exposure and disease, and as such, should not be adjusted for. Consequently, it is unlikely that the factors identified by Goodman et al. substantially confounded our results. On the other hand, we considered a large number of demographic and environmental factors that may be related to both PBDE serum levels and thyroid function, and we observed little confounding (Chevrier et al. 2010).

Goodman et al. also suggest that our results may be due to exposure and outcome misclassification based on *a*) the reference range that we used to determine subclinical hyperthyroidism; *b*) our use of different cutoffs for women in the second and third trimesters of pregnancy; and *c*) the fact that we measured PBDEs at one time point during pregnancy. As explained below, we believe that substantial misclassification is unlikely; even if misclassification did occur, it would most likely be nondifferential with regard to

exposure, which would be expected to bias associations toward the null rather than create spurious relationships.

Goodman et al. argue that in our study (Chevrier et al. 2010) we used inappropriate reference ranges to determine subclinical hyperthyroidism. Reference ranges for thyroid hormone are method, instrument, and gestational-age specific. The trimester-specific reference ranges that we used were developed by Quest Diagnostics on a Bayer ADVIA Centaur system (Siemens Healthcare Diagnostics, Deerfield, IL), the instrument used for our analyses; thus, they were appropriate. Reference ranges cited by Goodman et al., however, were based on studies that used different methods and instruments and/or that were conducted earlier in pregnancy (e.g., ≤ 21 weeks of gestation) (Haddow et al. 2004; Price et al. 2001; Stricker et al. 2007; as reviewed by Krassas et al. 2010).

Goodman et al. criticize our use of different reference ranges for women whose TSH was measured in the second and third trimesters of pregnancy. However, the National Academy of Clinical Biochemistry (Baloch et al. 2003), as well as authors cited by Goodman et al. (Krassas et al. 2010), recommend using trimester-specific reference ranges because thyroid hormone levels change during the course of pregnancy. Furthermore, we found inverse associations between PBDEs and TSH expressed continuously (Chevrier et al. 2010), demonstrating that the relationships are not due to the cutoff points used to dichotomize TSH.

Goodman et al. also believe that we should have taken multiple blood samples to determine exposure to PBDEs. The PBDE congeners that we measured, however, are highly persistent in humans (estimated half-lives of 2–12 years). In addition, PBDE serum concentrations measured at 27 weeks of gestation and at delivery were strongly correlated ($r = 0.82$ – 0.99 ; $p < 0.001$) among CHAMACOS women, suggesting that a single measurement is sufficient to determine exposure.

Goodman et al. state that the fact that congeners are intercorrelated leaves the impression that several congeners may be related to TSH. Correlation between the congeners was expected because they are components of the same commercial mixture (pentaBDE). Although identifying the specific congener(s) that may be related to thyroid hormone disruption is of scientific interest, it is of little relevance in terms of public health; relationships between any one of the measured PBDE congeners and thyroid hormone levels is of concern.

Finally, Pop et al. (1999) reported that small variations in maternal thyroid hormone during pregnancy were related with

altered child neurodevelopment. In our study (Chevrier et al. 2010), we reported a 37.7% reduction in TSH over the full range of total PBDEs and a 3.9-fold increase in the odds of subclinical hyperthyroidism among women in the fourth quartile of BDE-100 relative to those in the first quartile. These associations are neither “very small” nor are they within the reference range, as argued by Goodman et al.

PBDE serum concentrations in the CHAMACOS population (Chevrier et al. 2010) were similar to those of the general U.S. population, and observed associations may be stronger in populations with higher exposure. Although, additional studies are needed to confirm our findings and to evaluate the relationships between maternal subclinical hyperthyroidism and maternal and fetal health, we believe that our results merit consideration by policy makers as well as the bromine industry.

The authors declare they have no competing financial interests.

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REFERENCES

- Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, et al. 2003. Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. *Thyroid* 13(1):3–126.
- Chevrier J, Harley KG, Bradman A, Gharbi M, Sjödin A, Eskenazi B. 2010. Polybrominated diphenylether (PBDE) flame retardants and thyroid hormone during pregnancy. *Environ Health Perspect* 118:1444–1449; doi:10.1289/ehp.1001905 [Online 21 June 2010].
- Haddow JE, Knight GJ, Palomaki GE, McClain MR, Pulkkinen AJ. 2004. The reference range and within-person variability of thyroid stimulating hormone during the first and second trimesters of pregnancy. *J Med Screen* 11(4):170–174.
- Krassas GE, Poppe K, Glinooer D. 2010. Thyroid function and human reproductive health. *Endocr Rev*; doi:10.1210/er.2009-0041 [Online 23 June 2010].
- Pop VJ, Kuijpers JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ, et al. 1999. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. *Clin Endocrinol (Oxf)* 50(2):149–155.
- Price A, Obel O, Cresswell J, Catch I, Rutter S, Barik S, et al. 2001. Comparison of thyroid function in pregnant and non-pregnant Asian and western Caucasian women. *Clin Chim Acta* 308(1–2):91–98.
- Stricker R, Echenard M, Eberhart R, Chevailler MC, Perez V, Quinn FA. 2007. Evaluation of maternal thyroid function during pregnancy: the importance of using gestational age-specific reference intervals. *Eur J Endocrinol* 157(4):509–514.

ERRATUM

The November Science Selection article “Disinfection By-products and Bladder Cancer: Common Genetic Variants May Confer Increased Risk” [*Environ Health Perspect* 118:A491 (2010)] incorrectly stated that “Among individuals who carried both of the *GSTT1* and *GSTZ1* genotypes noted above (28% of study participants), those with the highest DBP exposure were at a 1.5 times increased risk of bladder cancer compared with carriers with the lowest DBP exposure.” Among individuals who carried both of the *GSTT1* and *GSTZ1* genotypes noted above (28% of study participants), those with the highest DBP exposure actually were at a 5.9 times increased risk of bladder cancer compared with carriers with the lowest DBP exposure. Risk was only 1.5 times higher with high versus low DBP exposure among study participants who lacked both genotypes. *EHP* regrets the error.